

Appl. No. 10/695,236
Amdt. dated February 9, 2005
Reply to Office action of November 10, 2004

Amendments to the Specification:

Please replace paragraph [0013] with the following amended paragraph:

5 [0013] Another object of the invention is to provide a flow cell design that provides the flexibility to increase the number of sample channels without ~~comprising~~ compromising the ability of the sensors within the flow cell to make accurate measurements.

Please replace [0034] with the following amended paragraph:

10 [0034] Referring now to the drawings, where similar parts are numbered the same, Figure 1 depicts a simple embodiment of the invention where the flow cell 10 comprises a substrate 20 having at least one sample channel 30 and at least one optical fiber channel holder 35 disposed therein. For the purpose of this application and the appended claims,
15 an optical fiber channel holder is a holder that is capable of achieving precision alignment and consistent tension on the optical fiber. At least one optical fiber 40 is disposed within each optical fiber channel holder 35. The optical fiber 40 has at least one grating 50 disposed therein. The optical fiber channel holder 35 is designed to come into contact with the sample channel 30 at the points along the optical fiber where each optical fiber
20 grating 50 is located. These points define a sensing area 55. At least one sample port 60 is positioned in an operable relationship to at least one sample channel 30 to permit introduction of a sample into the sample channel. A sample outlet 75 is in fluid connection with the sample channel 30 such that the sample is removed from the flow cell through the sample outlet 75. ~~Although two sample ports are depicted, it is~~
25 ~~understood that there need only be one sample port.~~ When the flow cell has ~~one sample port, no sample outlet,~~ the sample is introduced into and exits from the flow cell through the same sample port 60. The sample port 60 is positioned in an operable relationship to the sample channel 30 such that the sample may easily flow into the sample channel. In one embodiment of the invention, where the flow cell comprises more than one sample

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port, at least one sample port is plugged with a gas permeable material that allows air to escape as a sample is introduced into another sample port. Alternatively, a pump is attached to at least one sample port to serve as a means for either drawing or pushing the sample through the flow cell. Lastly, the sample port may serve as an exit port for the sample after it flows through the flow cell. Multiple sample ports may be employed when the user desires to introduce multiple samples into the flow cell. Alternatively, a pipette tip is formed on the sample port for drawing fluid samples into the sample channel and through the substrate. This is especially desirable when a microtiter plate arrangement is employed.

Please replace paragraph [0040] with the following amended paragraph:

[0040] Figure 3 depicts an alternative embodiment of the flow cell 10 comprised of three mating pieces. In this embodiment, there is an upper section 100 containing at least one sample channel (not shown) and at least one sample port 60. This portion is counter-sunk to permit critical alignment of the optical fiber channel holder 35 with the sample channel 30. In the middle section 110, there is the optical fiber channel holder 35 having the optical fiber 40 disposed therein. The optical fiber channel holder 35 is configured to allow a space defining a sensing area 115 where the grating portion of the optical fiber 40 is located. The optical fiber channel holder is designed such that the sensing area and flow cell walls are close to the fiber for diffusion purposes. The lower section 120 of the flow cell serves as a support or base for the assembly. As with the upper portion, the lower section 120 is also counter-sunk to permit critical alignment of the optical fiber channel holder 35 with the sample channel 30. The flow cell assembly is joined and held together by a fastener. Any fastener known to those of skill in the art may be used. Examples of such fasteners include but are not limited to: screws; nuts and bolts; male-female connectors that are fabricated as part of the substrate; rivets; welds; adhesives; straps; crimp connectors such as bent wire; bands fabricated from rubber, metal, plastic; and clamps such as C-clamps. The use of multiple mating pieces allows the user to

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modify the flow cell or reconfigure it. For example, an upper section containing a single sample channel having one sample port may be substituted with an upper section having multiple sample channels having either one or multiple sample ports. If desired, the upper section may also contain a sample outlet or multiple sample outlets so the sample is removed from the flow cell through an outlet other than the sample port. Alternatively, the middle section may be exchanged to match the number of sample channels of the upper section or may provide a single sensing area where many samples converge. When the need arises, one may incorporate various sealing means, such as gaskets, to prevent leakage. Because of the versatility afforded by having a piece-like structure, a flow cell kit is provided that allows the user to design custom flow cells depending on the application. The kit configuration makes the flow cell easy to clean. The ability to disassemble the flow cell easily allows for the user to apply various coatings to the cell that can be removed without causing damage to the flow cell. A flow cell comprised of mating pieces provides a significant advantage over the prior art flow cells because it is easy to clean; can be easily converted for a particular application; provides consistent manufacturing and test results; and provides the flexibility to increase the number of sample channels without compromising the measurements made in the sensing area.

Please replace paragraph [0041] with the following amended paragraph:

[0041] Figures 4 and 5 show alternative embodiments of the invention where the number of sample ports and sample channels are varied and the sample port serves as both an inlet and an outlet for the sample. In these configurations, the sample channel 30 terminates with a sample reservoir 37. This permits the sample to be contained within the flow cell after it has passed through the sensing area 55. Figure 4 depicts an embodiment where there is one sample port 60 and a plurality of sample channels 30. In this arrangement, the sample enters and exits the flow cell 10 through the sample port 60. The optical fiber 40 is disposed within the optical fiber channel holder 35. Sample measurements are made in the sensing area 55 where the optical fiber grating 50 is in

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close proximity to the sample channel 30. Figure 5 shows an alternative embodiment that allows samples to be mixed within the flow cell 10. In this embodiment, a plurality of sample ports 60 are provided but only one sample channel 30, terminating with a sample reservoir 37, is provided. The optical fiber 40 is disposed within the optical fiber channel holder 35. A plurality of samples are introduced through the sample ports 60, mixed in the sample channel 30, and detected in the sensing area 55 of the flow cell where the grating 50 is in close proximity to the sample channel. The mixed sample is removed from the flow cell through the sample ports 60 upon completion of the data collection process. Both figures depict a preferred embodiment where an optical fiber connector 45 is attached to an end of the optical fiber 40.

Please replace paragraph [0044] with the following amended paragraph:

[0044] Figures 11A and 11B depict how a flow cell array 125 is assembled by stacking various flow cell assemblies 10 together. Each flow cell 10 has a means for interlocking with another flow cell (not shown). In a most preferred embodiment of the invention, the flow cell has at least one sample outlet 75, at least one sample channel 30 (not shown), and 2, 8, 96 384, or 1536 sample ports. ~~In addition, each~~ Each flow cell has at least one sample port 60. Also depicted is a preferred embodiment where each optical fiber (not shown) terminates with an optical fiber connector 45. When there are multiple sample channels, each channel is spaced apart a distance of less than or about 9mm. This spacing makes the flow cell compatible with micro titer plates which are the sample plates used in life sciences research. The tip volumes and spacing between the tips are designed into the flow cell for microtiter interface. In addition, when the flow cell comprises mating pieces, quadrant sampling can be used to interface with high capacity plates such as 384 and 1536 micro titer plates (Figures 11A and 11B).